REMARKS/ARGUMENTS

Reconsideration of the above-identified application is respectfully requested. Claims 1-10 remain in the application.

The Invention

As noted in the specification, one of the major criteria for heart transplantation is to maintain viability of the heart for an extended period. It is known that using a University of Wisconsin isotonic solution that 18 hours of preservation in 4°C, no necrosis was evident in a heart, but apoptosis was present. Thus, the subject of this invention is the ability of the proposed preservation solution to block apoptosis so that preservation times can be extended. (Specification, p. 3). The ability of the solutions of the claimed invention to maintain the viability of a heart awaiting transplantation are clearly shown in the experimental section of the specification beginning on page 10. In summary, it is noted that apoptosis was found to be an important cell mediator for attenuating functional recovery in that 18 hours of preservation with the UW solution resulted in only 50-60 percent functional recovery with significant amounts of apoptosis cells in the myocardium. Blocking apoptosis with cyclosporin A resulted in the prolongation of viability to 18 and 24 hours. Thus, use of cyclosporin in the preservation solution prolongs myocardial function by maintaining ATP levels and blocks apoptosis, thereby preventing programmed cell death during donor heart preservation.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 6-10 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite by the phrase "which extends the life of the heart" and thereby failing to clearly set forth the metes and bounds of the patent protection desired.

Claim 6 has been amended to delete the objected to phrase and now states "A method for preserving and storing a heart awaiting transplantation comprising". This amendment to Claim 6 more accurately reflects the actual method. It is, therefore, believed that this rejection has now been overcome.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 1-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Massoudy *et al.* The Examiner states that "Massoudy *et al.* teach the use of a Krebs-Henseleit buffer containing cyclosporin at a 0.8 micro molar concentration to effect cardio-protection in isolated hearts."

As opposed to the *reperfusion regimen* disclosed in Massoudy *et al.*, the solutions and methods of the present invention are directed to solutions for the preservation and storing a heart and methods for preserving and storing a heart awaiting transplantation. It was found that when cyclosporin is added to the preservation and storing solution (1) to preserve the mitochondrial function, which it does so by maintaining adenosine triphosphate (ATP) levels, and (2) to block apoptosis and prevent program cell death.

The authors of the Massoudy *et al.* article are interested in reperfusion injury in hearts that are "preserved" for 15 minutes and attribute this to a nitric oxide-dependent mechanism mediated by endothelia *(see page 537, left column)*. Reperfusion injury involves changes in mitochondrial function which results in limitation of ATP production and loss of membrane function to regulate ion changes in the cell. These changes prevent extending heart preservation past 12 hours without causing irreversible injury. Once the 18 hour point of preservation is reached, significant damage has occurred that limits the total recovery of the heart as measured by functional and historilogical changes. Permanent damage is found to be associated by production of apoptotic cells in the heart. On the other hand, the studies of the claimed invention have shown that hearts may be preserved and stored for 18 to 24 hours while awaiting transplantation.

When cyclosporin A (which inhibits apoptosis by stabilizing the mitochondrial membrane) is added to the preservation solution, complete recovery is possible after preservation at 18 and 24 hours. Since Massoudy *et al.* are not interested in heart preservation and maintain their 15 minute preservation at 37°C, the relevancy of their findings is hardly pertinent to the claimed invention. Massoudy *et al.*'s findings on reperfusion injury, while interesting and may plan an acute role in cardiac ischemia, have little or no effect on the observations that the claimed invention seeks to protect.

Therefore, it is respectfully submitted that Massoudy *et al.* does not anticipate either solution Claims 1-5 or method Claims 6-10, as there is no indication in Massoudy *et al.* that there is the possibility of preserving a heart for transplantation much less for up to 24 hours.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Raymond ('462), Jurado *et al.* and Massoudy *et al.* The Examiner states that each of the three references

> teach the claimed Krebs-Henseleit buffer as well known in combination with various pharmaceutical carriers and expedience in dosage form. The medicaments are taught as useful for extending the psychological integrity of isolated organs to include hearts, as herein claimed. Claims 1-10, and the primary references, differ as to:
>
> (1) the concomitant employment of these medicaments, and
>
> (2) specific benefits residing in the administration of these medicaments.
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> *Office Action dated 8/4/03 at page 4.*

The Examiner then states that

> It is generally considered *prima facie* obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea of combining them flows logically from their having been used individually in the prior art. As shown by the recited teachings, the instant claims define nothing more than the concommoditant use of ingredients conveniently employed for extending the psychological integrity of isolated organs employed for transplantation. It would follow that the recited define *prima facie* obvious subject matter. *Cf. In re Kerhoven*, 626, F.2d 848, 205 U.S.P.Q. 1069 (CCPA 1980).
>
> Claims 6-10 specifically requires the envisioned pharmaceutical composition to maintain the physiological integrity of organs removed for transplantation. Raymond ('462), Jurado *et al.* and Massoudy *et al.* teach the claimed compound individually, and concommitedently are useful for providing this benefit, although not specifically reciting the benefit of the extended "the life of the heart". The skilled artisan would have been possessing the cardio-protective benefits taught by Raymond ('462), Jurado *et al.* and Massoudy *et al.* as encompassing those benefits and visions therein. *Office Action dated 8/4/03 at pages 4-5.*

The patent to Dr. Raymond, U.S. Patent No. 5,693,462, is directed to a preservation solution that includes an isotonic solution for perfusing and storing a heart at room temperature

for up to at least 24 hours while waiting transplantation. To this point, the preservation solution are similar to that claimed. The Raymond preservation solution also requires from 1.0 μm to about 5.0 μm of an amiloride-containing compound and a small amount of adenosine. The Raymond preservation solution is designed to prevent various mechanisms which cause injury to the organ. These solutions (1) prevent or restrict intercellular acidosis, (2) prevents expansion of intracellular space, (3) prevents injury from oxygen-derived free radicals, (4) enables the regeneration of high energy phosphate compounds during reperfusion, and (5) sustains the appropriate metabolic requirement. *Col. 5, lines 11-20.* Thus, the preservation solution described in Raymond that includes amiloride and adenosine do not prevent ATP loss inhibiting apoptosis as shown by the claimed invention. Furthermore, there is no teaching whatsoever in Raymond that other components should be substituted for amiloride or adenosine. Furthermore, neither of these two components are present in the claimed preservation solution and there is certainly no indication from Raymond or the two secondary references that amiloride and adenosine should be removed from the Raymond solution to teach the claimed preservation solutions.

The article to Jurado *et al.* discusses studies that affect the cardiac muscle after heart transplantation. Jurado *et al.* provide a daily dose of CsA in a cremophor vehicle. Jurado *et al.* has nothing whatsoever to do with the preservation of a heart awaiting transplantation.

The other secondary reference that of Massoudy *et al.* has been thoroughly discussed above with respect to the 102 rejection and the arguments presented there are equally applicable to this rejection.

It is respectfully submitted that the claims are not obvious over Raymond ('462), Jurado *et al.* and Massoudy *et al.* First of all, the Examiner states that the isotonic buffer solution of the claimed invention is the same for all three cited references. In fact, Jurado *et al.* does not use an isotonic solution. Raymond does not use a cyclosporin A. Jurado *et al.* is for treatment after a heart has been transplanted. Furthermore, neither Raymond, Jurado *et al.*, nor Massoudy *et al.* are intended to reduce apoptosis. Thus, the idea of combining the reference does not flow logically for their having been used individually in the prior art. The instant claims are not merely a concomitant use of ingredients from the prior art as there is no teaching in any of the

cited references of the results obtainable from the claimed invention. While it might be *prima facie* obvious to combine two compositions, each of which are taught by the prior art, to be useful for the same purpose in order to form a third composition such is not the case with the claimed invention as the purpose of the claimed invention is not taught in any of the references. This fact distinguishes the present situation from that of *In re Kerhoven* relied upon by the Examiner.

In conclusion, mere knowledge that combining an isotonic solution with cyclosporin A are useful in extending the psychological integrity of hearts does not suggest anything about the effect of substantially reducing apoptosis during preservation of hearts. Consequently, one skilled in this art working at the time of the invention on the problem of how to preserve the viable life of a heart awaiting transplantation would not have been motivated or guided by the cited prior art to arrive at the process claimed in Claims 6-10 or the solution of Claims 1-5.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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